DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-12 and 19-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Instant independent claim 1 recites the limitation "wherein said buffer solution is an acetate buffer solution containing 0.044 to 15 mM acetate or a citrate buffer solution containing 3.87 mM or less citrate". The specification lacks any description that supports the limitation of an acetate buffer containing 0.044 – 15 mM acetate. The range of 0.044 – 15 mM acetate introduces new matter that includes levels not conveyed in the specification.

At page 13, lines 24-26, Applicant recites, "It was, however, common in injectable products to include sodium acetate trihydrate at levels between 0.00006-0.2%. The 0.07% level used in the formulations of Example 1 is well within this range".

This is support only for sodium acetate trihydrate at levels between 0.00006-0.2% (0.044 - 0.2%), not acetate per se.

At page 13, lines 26-27, Applicant further states, "It was also known that citrate buffers found in inhalation products were present at levels that did not exceed 0.1%". Claim 1 recites the limitation, "3.87 mM or less citrate". It would appear that "or less citrate" also introduces new matter. There is, however, support for 3.87 mM citrate found at page 14, lines 5-8. New matter includes not only the addition of wholly unsupported subject matter, but may also include adding specific percentages or compounds after a broader original disclosure, or even the omission of a step from a method. See 706.03(o) New Matter [R-3].

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 5-12 and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Asmus et al.** (Stability of Frozen Methacholine Solutions in Unit-Dose Syringes for Bronchoprovocation. Chest 121:1634-1637 (May 2002)) and **Watson et al.** (Effect of pH on the stability of methacholine chloride in solution. Respiratory Medicine (1998) 92,588-592) and "**website**" (Practical Engineering Data & Tools for Medical Device Professionals: Selecting a Sterilization method (2001) http://web.archive.org/web/20030112130541/http://engineeringreference.com/Sterilization/select+sterilization.htm) in view of **FDA** (http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm) or **ScienceLab.com**, Material Safety Data Sheet: Sodium Acetate.

Asmus et al. teach a formulation of methacholine chloride wherein the concentration of methacholine is less than 0.25 mg/mL (see Abstract), sodium chloride is used as a diluent (see Abstract), the pH is from 4 to 5 (see Abstract) wherein the reference is directed to stabilizing the solution and teaches that the pH should be slightly acid since pH levels above 6 encourage hydrolysis of the solution and loss of potency (see page 1634) as well as directed to a process of making a sterile solution (see Materials and Methods on page 1635) which are further stored in plastic syringes (see Results page 1636). Asmus et al. do not teach a methacholine solution comprising acetate or citrate.

Watson et al. teach a methacholine chloride solution comprising sodium chloride (see Introduction page 588) and acetate at a concentration of 0.02M (see page 589, col. 1) wherein the reference further teaches that methacholine rapidly decomposes due to

hydrolysis under basic conditions (see Discussion page 591) and that being the basis of studying varying buffers and pHs which leads one of ordinary skill in the art to vary and optimize the concentration of acetate depending on the solution variables and desired resultant pH. Watson et al. also teach that phenol (considered a preservative since it is inhibiting contamination) can be added to the solutions to inhibit microbial growth (see Discussion page 592) thereby encouraging sterile solutions. The Watson reference does not expressly teach the claimed buffer amounts.

The website teaches a process for sterilizing liquid products comprising aseptic processing and filtration (see item 5). It further explains that many liquid pharmaceutical products cannot withstand thermal sterilization and that such are relegated to aseptic filtration and then filled into presterilized containers such as vials, ampoules or syringes (see item 5).

FDA teaches that the sodium citrate maximum level in a solution for inhalation is 0.6%. In addition, at page 4, ScienceLab.com teaches that sodium acetate in solution is a respiratory irritant.

One of ordinary skill in the art would have been motivated to combine the above references because Asmus et al. and Watson et al. are both directed to stable solutions of methacholine. Moreover, both teach that pHs over 6.0 lead to destabilization and hydrolysis of the methacholine, therefore, suggesting a lower pH, which Watson et al. teach by adding acetate to the solution. One of ordinary skill in the art would be motivated to make an inhalable solution comprising methacholine in a buffer solution comprising acetate or citrate levels that are within FDA approved levels. The skilled

artisan would have additional motivation to make the solution comprising a bronchoconstrictor such as methacholine with lower levels of acetate since, because, as taught by ScienceLab.com, sodium acetate is a respiratory irritant. The skilled artisan will be further motivated if the composition is administered to asthmatic patients. Both Asmus et al. and Watson et al. teach sterile solutions since the solution will be inhaled by a patient, which directs one of ordinary skill in the art to a method of sterilization. The Practical Engineering reference specifically teaches that liquid pharmaceuticals can be sterilized by aseptic filtration since they cannot withstand thermal sterilization. Therefore, one of ordinary skill in the art would expect a successful sterilization process by employing the Practical Engineering reference. Thus, the combined references teach and make prima facie obvious how to use the claimed invention at the time that it was made.

Response to Arguments

Applicant asserts that the methacholine chloride solutions disclosed in Watson cannot be considered to be "inhalable" because the acetate and citrate are too high according to FDA guidelines. However, the Federal Circuit has reiterated that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States. FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. See MPEP 2107.01 [R-5] III. Applicant

further asserts that Watson teaches away from the use of less buffer; thus, the skilled artisan would have no reason to lower the amount of buffering agent as less buffering capacity and lower stability would have been expected. The strength of the buffer capacity is not commensurate in scope with the claim. Applicant is claiming the amount of acetate or citrate that can be in the solution not what the buffer capacity is. Furthermore, Applicants have not demonstrated that buffering capacity is critical to the stability of methacholine. The art appreciates that the pH value is critical for stability of methacholine. Applicant hasn't provided comparative data demonstrating the criticality of buffering capacity. Even at the least, the ordinary skilled artisan would be motivated to try different buffering capacities to obtain the most cost effective buffered solution (i.e. if less buffer will do the job, the solution is cheaper to manufacture, and thus, this provides motivation for experimenting with lower amounts of buffer). There is an expectation in the art that as long as the pH is in the range of 4 to 5 that the methacholine solution will predictably remain stable.

Applicant's assertions are not persuasive. The Office holds the position that one of ordinary skill in the art would be motivated to decrease the amounts of the acetate or citrate levels in the old composition to make a composition comprising levels within acceptable levels of pharmaceutically acceptable buffering agents as provided by government regulatory agencies. Since it is known that sodium acetate is a respiratory irritant, the skilled artisan would be motivated to decrease the amount of sodium acetate in a composition for inhalation.

The skilled artisan would have recognized the desirability to make a solution of the bronchoconstrictor, methacholine, in a stable solution at a pH level between 4 to 6 as taught by Watson and Asmus using levels of the acetate or citrate buffer taught by Watson that are low enough to not contribute to respiratory irritation such as bronchoconstriction and are within the FDA guidelines.

Applicant refers to Tables 9 - 26 of the instant specification as support for unexpected results for the stability of the methacholine solution. A proper showing of unexpected results is not disclosed in the specification. These tables only describe the stability results for methacholine solutions within Applicant's claimed acetate and citrate buffer parameters. There are no side-by-side comparisons of Applicant's invention and that disclosed in the prior art under the same conditions to provide a showing of unexpected results.

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRIS E. SIMMONS whose telephone number is

(571)272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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